Online Supplemental Data

Presenting Clinical features				
	Patient 1	**Patient 2**	**Patient 3**	**Patient 4**
Sex	Male	Female	Female	Male
Age of 1st clinical manifestations of myelopathy	11 m	27 m	11 m	24 m
Initial presenting symptoms of myelopathy	Hypotonia and regression of ambulatory motor skills followed by gait spasticity with bilateral lower extremity paraparesis.	Hypotonia and regression of ambulatory motor skills, followed by gait spasticity and bilateral lower extremity paraparesis.	Hypotonia and delayed onset of ambulatory motor skills followed by gait spasticity and bilateral lower extremity paraparesis.	Hypotonia and delayed onset of ambulatory motor skills followed by gait spasticity and bilateral lower extremity paraparesis.
Perinatal history	"placental variant" detected by prenatal ultrasound. Spontaneous vaginal delivery at 42 w gestation. Maternal age at birth 30 years. 90th percentile for height and weight. Head circumference 97th percentile. No dysmorphology.	Unavailable.	Caesarean section at 37 w gestation for breech presentation.	Pre-eclampsia. Vaginal delivery at 36 w gestation. Nystagmus and bilateral subdural hygromas.
Family history	Mother and maternal aunt have multiple vascular birthmarks. No consanguinity. Ethnicity German/English/Scottish on paternal side and Finnish/German/Irish on maternal side.	Unavailable.	Mother had 2 miscarriages at 8 to 10 w gestation.	Unremarkable.
Physical findings	Multiple cutaneous café au lait spots on trunk. Normal hearing and vision.	Unavailable.	0.5 cm hyperpigmented macule on dorsum of left hand. Eczema.	Bell's palsy and bilateral cataracts two years after onset of myelopathy.

Laboratory findings				
	Patient 1	**Patient 2**	**Patient 3**	**Patient 4**
Electromyography and nerve conduction studies	Exam at 22 and 26 m of age show no consistent abnormality.	Not performed.	Normal at 18 m of age.	Not performed.
Cerebrospinal fluid	Normal protein, glucose and cell counts. At age 16 m, and 26 m showed elevated lactate	Normal protein, glucose and cell counts.	Normal protein, glucose and cell counts. At 24 m Pyruvate levels elevated (2.96). Non-specific low values for	Protein, glucose and cell counts normal.

	levels- 3.4 and 3.9 millimoles/L respectively. Normal levels of neopterin and biopterin. Amino acid, neurotransmitters, myelin basic protein, Aquaporin 4, oligoclonal bands and IgG normal.		taurine, glycine, valine, isoleucine, leucine and ornithine. Multiple IgG bands, same as in serum. Lactate levels normal.	
Echocardiography	Two normal echocardiograms documented.	Unavailable.	Unavailable.	Unavailable.
Serum lactate	Normal.	Unavailable.	Unavailable.	Unavailable.
Serum creatine phosphokinase	Normal.	Unavailable.	Unavailable.	Unavailable.
Endocrine and metabolic profiles	Normal.	Unavailable.	Unavailable.	Unavailable.
Serum transaminase elevation	Transient elevation of serum transaminases in late pre-terminal stage of clinical course.	Mild serum transaminase elevation late in clinical course.	Not available.	Not reported.
Hematological abnormalities	No abnormalities.	Not available.	No abnormalities.	Microcytic anemia.

MR imaging				
	Patient 1	**Patient 2**	**Patient 3**	**Patient 4**
Spinal cord abnormalities	Hyperintense T2 signal abnormality in central cord, anterior > posterior. Gadolinium enhancement of cord. Progressive cord expansion over 10-month period. No hemorrhage or calcification.	Hyperintense T2 signal abnormality in central cord, anterior > posterior. Gadolinium enhancement of cord. Cord expansion. No hemorrhage or calcification.	Hyperintense T2 signal abnormality in central cord, anterior > posterior. No cord enhancement. Cord expansion. No hemorrhage or calcification.	Hyperintense T2 signal abnormality in central cord, anterior > posterior. No cord enhancement. Cord expansion. No hemorrhage or calcification.
Anatomical extent of spinal cord abnormalities	Ventral medulla, cervical cord, thoracic cord and conus.	Ventral medulla, cervical + thoracic cord.	Ventral medulla, cervical cord, thoracic cord and conus.	Ventral medulla, cervical cord, thoracic cord and conus.
Abnormal vascular findings	Tortuous and dilated vasculature surrounding cervical cord, lower thoracic cord and conus on T2 weighted images,	Tortuous and dilated vasculature surrounding lower thoracic cord and conus on T2 weighted images.	Tortuous and dilated vasculature surrounding cervical cord, lower thoracic cord and conus on T2 weighted images.	Tortuous and dilated vasculature surrounding lower thoracic cord and conus on T2 weighted images.

	progressively worsening over 10-month period and becoming more accentuated in cervical and thoracic segments. Ventral > dorsal.	Ventral > dorsal.	Ventral > dorsal.	Ventral > dorsal.
Supratentorial findings	Mild diffuse parenchymal volume loss and commensurate ex vacuo enlargement of cerebral ventricles and cortical sulci. Diffuse intracranial arterial ectasia involving intracranial internal carotid arteries, middle cerebral arteries, vertebral arteries, basilar artery and bilateral posterior cerebral arteries. Two small arachnoid cysts- 1) anterior left frontal convexity. 2) anterior wall of left middle cranial fossa. Magnetic resonance spectroscopy shows lactate peak in left parietal white matter.	Normal. Magnetic resonance spectroscopy normal.	Normal. Magnetic resonance spectroscopy normal	Symmetrical T2 weighted signal hyperintensity and T1 weighted signal hypointensity in the anterior edge of the pons, pontine raphe, and middle cerebellar peduncles. Mild diffuse parenchymal volume loss and commensurate ex vacuo enlargement of cerebral ventricles and cortical sulci. Magnetic resonance spectroscopy not performed.

Catheter directed angiography findings				
	Patient 1	**Patient 2**	**Patient 3**	**Patient 4**
Extrinsic spinal cord arteries (anterior spinal artery, radiculomedullary arteries, posterolateral spinal arteries, radiculopial arteries)	Marked ectasia of anterior spinal artery. Marked ectasia of dominant lower thoracic radiculomedullary artery with moderate ectasia of multiple additional radiculomedullary arteries. Descending ramus of anterior spinal artery much larger than ascending ramus of anterior spinal artery. Mild enlargement of posterolateral spinal arteries and corresponding radiculopial arteries.	Marked ectasia of anterior spinal artery. Marked ectasia of dominant lower thoracic radiculomedullary artery with moderate ectasia of multiple additional radiculomedullary arteries. Mild enlargement of posterolateral spinal arteries and corresponding radiculopial arteries.	Marked ectasia of anterior spinal artery. Marked ectasia of dominant lower thoracic radiculomedullary artery with moderate ectasia of multiple additional radiculomedullary arteries. Descending ramus of anterior spinal artery much larger than ascending ramus of anterior spinal artery. Mild enlargement of posterolateral spinal arteries and corresponding radiculopial arteries.	Marked ectasia of anterior spinal artery. Marked ectasia of dominant lower thoracic radiculomedullary artery with moderate ectasia of multiple additional radiculomedullary arteries. Descending ramus of anterior spinal artery much larger than ascending ramus of anterior spinal artery. Mild enlargement of posterolateral spinal arteries and corresponding radiculopial arteries.

Intrinsic spinal cord arteries (central sulcal arteries)	Marked ectasia of central sulcal penetrating arteries.	Marked ectasia of central sulcal penetrating arteries.	Marked ectasia of central sulcal penetrating arteries.	Marked ectasia of central sulcal penetrating arteries.
Intrinsic spinal cord veins	Not perceptible.	Not perceptible.	Not perceptible.	Not perceptible.
Extrinsic spinal cord veins	Mild to moderate ectasia of perimedullary veins.	Mild to moderate ectasia of perimedullary veins.	Mild to moderate ectasia of perimedullary veins.	Mild to moderate ectasia of perimedullary veins.
Spinal cord parenchymal hyperemia	Marked diffuse homogenous spinal cord hyperemia with brisk appearance of parenchymal draining veins.	Marked diffuse homogenous spinal cord hyperemia with brisk appearance of parenchymal draining veins.	Marked diffuse homogenous spinal cord hyperemia with brisk appearance of parenchymal draining veins.	Widespread in-homogenous spinal cord hyperemia with brisk appearance of parenchymal draining veins.
Intracranial abnormalities	Moderate diffuse ectasia and tortuosity of intracranial internal carotid arteries, middle cerebral arteries, vertebral arteries, basilar artery and bilateral posterior cerebral arteries.	Catheter directed cerebral angiography not performed.	Catheter directed cerebral angiography not performed.	Catheter directed cerebral angiography not performed.

Clinical course				
	Patient 1	**Patient 2**	**Patient 3**	**Patient 4**
Clinical progression and timeline of motor decline	Walked at 11 m of age but regressed to crawling by 13 m of age. Subsequently had spastic gait with bilateral lower extremity paraparesis. Progression to minimal movement of upper extremities, unable to hold up head and worsening respiratory insufficiency by 23 m of age.	Hypotonia and regression of ambulatory motor skills at 27 m of age. Subsequently had spastic gait with bilateral lower extremity paraparesis. Progression to quadriparesis by 61 m of age.	Hypotonia and constipation at 11 months of age with delayed onset of ambulatory motor skills. Subsequently had spastic gait with bilateral lower extremity paraparesis. Progression to quadriparesis by 18 m of age.	Slowly progressive bilateral lower extremity spastic paraparesis worsening over the course of 1 year from time of initial presentation. Thereafter the patient showed stabilization of leg weakness with slow persistent worsening of lower extremity spasticity over subsequent 2-3 years. At last follow up (5 years and 9 months of age) the patient ambulates with crutches and has moderately frequent incontinence.
Disease Modifiers	Neurologic deficits markedly aggravated by anesthesia and febrile illness with gradual recovery over several days.	Neurologic deficits markedly aggravated by anesthesia and febrile illness with gradual recovery over several days.	Not noted.	Not noted.
Treatments	Course of high dose steroids. Surgical ligation of dominant lower thoracic radiculomedullary artery (Left T11) near junction with anterior spinal artery	Physical and occupational therapy.	Physical and occupational therapy.	Vitamin E, physical and occupational therapy. Initially treated with carnitine but stopped due to no evident effect and costs,

	with intraoperative neurophysiologic monitoring and fluorescein angiography.			
Response to treatment	Steady persistent neurological decline despite course of high dose steroids. Characteristic decline in neurologic function after general anesthesia for surgery but returned to baseline function within 3 weeks. Died 5 weeks after surgery from complications of aspiration pneumonia.	Steady persistent neurological decline despite physical and occupational therapy.	Stabilized.	Slow persistent neurological decline.
Clinical Outcome	Died 14 months after onset of symptoms from complications of aspiration pneumonia.	Died 73 months after onset of symptoms from complications of lactic acidosis and progressive encephalopathy. Non-contrast CT scan of head showed diffuse cerebral edema (Supplementary figure I, Online supplement 2).	Independently ambulatory at last follow up more than one year after symptom onset.	Ambulatory with a walker at last follow up more than one year after symptom onset.

Pathology and DNA analysis				
	Patient 1	**Patient 2**	**Patient 3**	**Patient 4**
Histopathology of ectatic spinal artery	30 mm long x 10 mm wide segment of dominant lower thoracic radiculomedullary artery stained with Hematoxylin and Eosin and Trichrome. Gross normal. Microscopic shows intact and continuous internal elastic lamina with thin adventitial sheath. No evidence of vascular inflammation.	No surgical specimen obtained.	No surgical specimen obtained.	No surgical specimen obtained.
DNA analysis of blood samples	3 gene HHT and CM-AVM panels negative. Mitochondrial DNA sequencing and deletion analysis covering 37 different genes was negative. Whole exome sequencing and Focused sequence analysis targeting over 1500 genes involved in mitochondrial function and numerous genes regulating vessel wall biology and homeostasis revealed no confirmatory evidence of pathological mutation. *See footnote.	Not available.	3 gene HHT and CM-AVM panels negative.	3 gene HHT panel negative. WES of nuclear DNA revealed a pathological germline mutation in one allele of the TFRC gene (p.Gly238 Asp variant inherited from mother and p.Pr0314 Leu variant inherited from father).

DNA analysis of ectatic spinal artery tissue	Whole exome sequencing and Focused sequence analysis targeting genes regulating vessel wall homeostasis revealed no confirmatory evidence of pathological mutation. *See footnote.	No surgical specimen obtained.	No surgical specimen obtained.	No surgical specimen obtained.

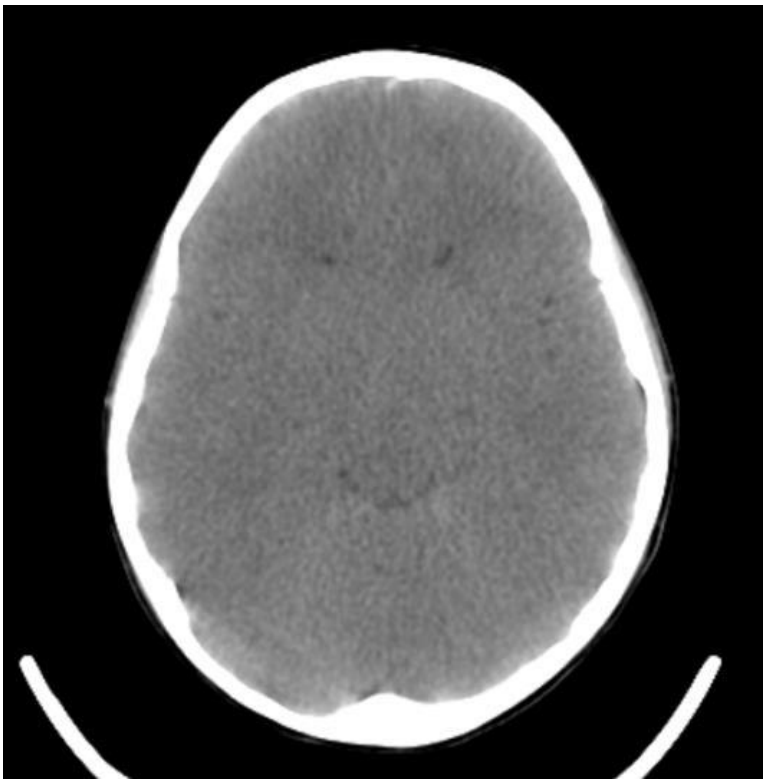
***** In patient 1, a heterozygous sequence variant detected in the RAC2 gene (encodes a member of Ras protein superfamily of GTPase signaling proteins that control cytoskeletal morphology) was present in radiculomedullary arterial tissue, but not in blood from the same patient, however it was not considered to be consistent with strong evidence of a pathological mutation because the sequence variant was common in the general population and was found deep within an intron.

In patient 1, a variant in the APOBEC1 gene (encodes an Apolipoprotein B mRNA editing enzyme involved in arterial wall homeostasis) was found to be heterozygous in blood and homozygous in radiculomedullary artery tissue from the same patient, however since the variant was located deep within the intron of the gene, and was common in the general population, it was not considered to be consistent with strong evidence of a pathological mutation.

Patient 1 was found to be a carrier of a recessive splice donor variant in the PCK2 gene, and a recessive missense variant in the QRSL1 gene. Notably homozygous defects in these genes have been associated with mitochondrial disease.

Supplementary Figure I: Metabolic encephalopathy.

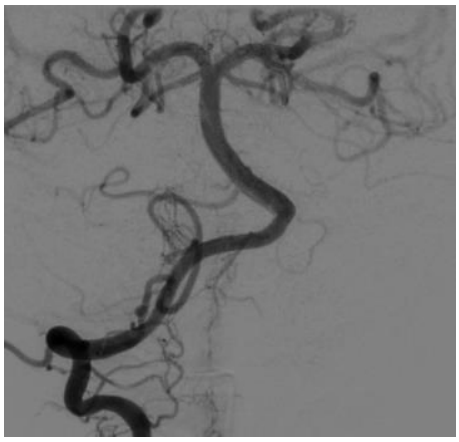
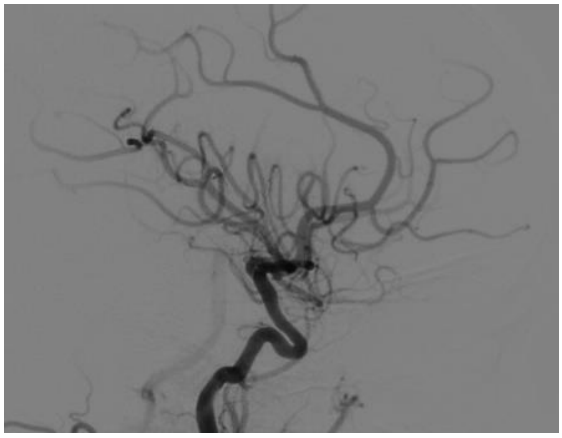
Non-contrast axial computerized tomographic image obtained in the terminal encephalopathic phase of patient 2 shows diffuse loss of gray-white matter differentiation. There is effacement of cortical sulci, subarachnoid cisterns and the frontal horns of the lateral ventricles consistent with widespread cerebral edema.

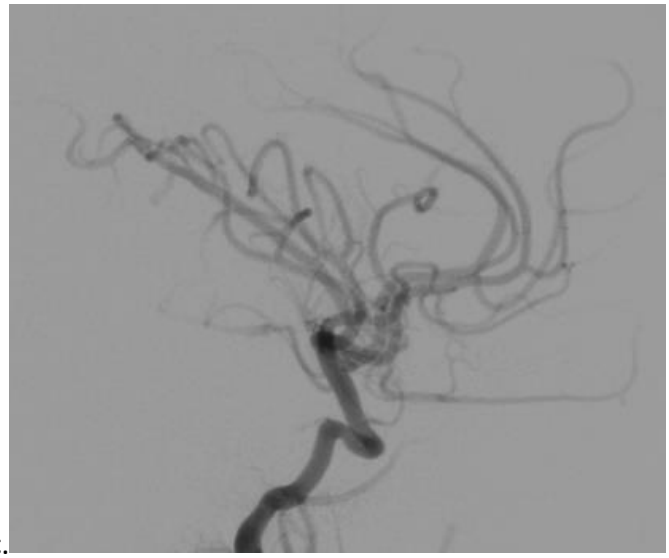


Supplementary Figure II a, b, c: Cerebral arterial ectasia.
(a) Frontal projection of right vertebral artery angiogram in early arterial phase from patient 1 shows ectasia of right vertebral artery, basilar artery and posterior cerebral arteries.

(b) Frontal projection of right common carotid artery angiogram in early arterial phase from patient 1 shows ectasia of intracranial right internal carotid artery.

(c) Frontal projection of left common carotid artery angiogram in early arterial phase from patient 1 shows ectasia of intracranial left internal carotid artery.

a.  b. 

c. 

Supplementary Figure III: Ectatic central sulcal penetrating arteries.
Early arterial phase of left T11 posterior intercostal artery angiogram, patient 1. The slightly oblique frontal projection shows a markedly enlarged, tortuous anterior spinal artery (asterisks) and prominent central sulcal penetrating arteries profiled (black arrows), and on end (white arrows).